DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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CBER–00-018

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

WARNING LETTER

MAR 2 3 2000

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Demetrios Demetriades, M.D., Ph.D.
University of Southern California
Medical Center
1200 North State Street
Los Angeles, California 90033

Dear Dr. Demetriades:

During the period from November 15 to December 20, 1999, Ms. Cheryl LeGrand and Mr. Richmond Yip, investigators with the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study using ——————————— in human subjects with hemorrhage due to trauma. The clinical study is sponsored by ——————— The inspection was conducted under FDA's Bioresearch Monitoring Program that includes inspections designed to monitor the conduct of clinical research involving investigational drugs.

FDA has reviewed your letter dated January 11, 2000, in which you responded to the Form FDA 483 – List of Inspectional Observations ("Observations") issued to you at the end of the inspection. Your response purports to explain the source of some of the deviations and proposes corrective actions. Our comments regarding your explanations will be addressed below. Corrective actions addressed in your letter may be referenced in your response to this letter, as appropriate.

Based on information obtained during the inspection, we have determined that you have violated regulations governing the proper conduct of clinical studies involving investigational new drugs and the protection of human subjects, as published in Title 21, Code of Federal Regulations, Parts 312 [21 CFR 312] and 50 [21 CFR 50], respectively. The outcome of the FDA audit/inspection raised concerns about the quality of your clinical research.

In accordance with 21 CFR 312.60 and Part 50, an investigator is responsible for ensuring that an investigation is conducted according to the signed investigational statement, the investigational plan (protocol), and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation. Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of investigational new drugs for the reasons listed below. The applicable provisions of the CFR are cited for each violation.

1. **Failure to ensure that the investigation is conducted according to the investigational plan (protocol). [21 CFR 312.60]**

   Our inspection revealed that several important protocol directives were not followed, resulting in significant deviations from the protocol.

   a. According to the protocol, each subject was to receive ——— ——— Several subjects were not administered the study drug over the period specified in the protocol. For example:

      i. Subjec ———– The second ——— study drug infusion was administered in approximately 2 hours during an operation on 2/21/99. The case report form (CRF) documents that the subject began the second infusion of the study drug on 2/21/99 at 18:01 and completed on 2/21/99 at 20:00.

      ii. Subjec —— – The first ——— study drug infusion was given in approximately 5.5 hours. The CRF reports that the subject began the first study drug infusion on 6/22/98 at 10:25 and completed 6/22/98 at 16:10; however, the Physician's Patient Clinical History sheet records a date on 6/22/98 at 10:00 and 6/23/98 at 08:00. The second —— study drug infusion was administered over 12 hours instead o ——— The CRF records that the second ——— time period started on 6/23/98 at 09:20 and completed on 6/23/98 at 21:00.

      iii. Subjec ———– The firs ——— study drug infusion was given in approximately 15 hours. The subject was administered the first ——— study drug infusion on 8/13/98 at 18:05 and completed on 8/14/98 at 09:30.

      iv. Subjec —— – The first ——— drug infusion was administered in approximately 4.5 additional hours. The Intake & Output Flowsheet records that the subject began the first study drug infusion on 4/27/99 at 04:20 and completed on 4/28/99 at 09:00. The secon ——— drug infusion was administered 2 hours short. The Intake & Output Flowsheet records that the secon ——— drug infusion began on 4/28/88 at 09:01 and completed on 4/29/99 at 07:00.

v. Subject ——— - The Physician's Patient Clinical History sheet dated 12/16/98 records that the first ——— drug infusion was stopped one hour early.

vi. Subject ——— – An additional 45 ml of the study drug was infused over ——— hours. The Intake & Output Flowsheet (printed April 1, 1998) records that infusion of the study drug started on 3/29/98 at 23:45 and ended on 4/1/98 at 08:00.

Your response letter dated January 11, 2000, states that it was not possible to infuse additional study drug, since the volume of the study drug was standard and a pump controlled the volume and time of study drug infusion. However, source documents do not accurately reflect the scheduled completion of the study drug infusion. The inspection revealed that information on study drug administration differed from other source documents.

Dr. Esteban Gambaro, Study Coordinator, stated that sometimes the start/stop times of the study drug infusion would be pre-filled/recorded on the source documents. We view this practice to be unacceptable. We remind you that data entries should not be recorded onto source documents prior to actual events. Pre-recording data is not an acceptable record keeping practice.

b. The protocol requires commencement of study drug administration within ——— from time of traumatic incident. The following subjects were randomized after the ——— recruitment window of eligibility:

i. Subject ——— – The DEM Trauma Nursing Record documents the subject arrival date as 9/19/98 and the assessment time as 00:18. According to the Physician's Patient Clinical History sheet, the subject drug infusion did not start until 12:30 on 9/19/98. There was no documentation in the Emergency Medical Service report about the time of the traumatic incident.

ii. Subject ——— – The CRF documents the traumatic incident as occurring at 01:40 on 9/13/98 and the subject received the first study drug infusion on 9/13/98 at 14:15.

iii. Subject ——— - The assessment time reported in the DEM Trauma Nursing Record was used as the traumatic incident time at 01:39 on 10/31/98. However, the Trauma Patient Summary sheet dated 10/31/98 records the arrival time to the hospital at 01:16. The first ———infusion began at 13:30 on 10/31/98.

Your response letter dated January 11, 2000, states that exceptions were granted previously for extensions beyond the —— window. There is neither documentation that indicates that the sponsor granted extensions beyond the —— recruitment window for the subjects listed above, nor documentation that indicates that you discussed this matter with the sponsor. The monitor of the study documented in a letter issued to you on December 23, 1998, that four subjects —————————— were enrolled outside the —— window without prior approval.

c. For those subjects who were granted enrollment into the study within —— —— from time of traumatic incident, at least 2 subjects were observed to be enrolled beyond the —— recruitment window.

   i. Subjec —— – The Telephone Communication Form of 4/1/98 documents that permission was granted not to exceed —— (08:21). However, the CRF records that the subject received the study drug beginning 09:30.

   ii. Subjec —— – The traumatic incident was reported on the CRF to occur on 9/16/98 at 23:00. The Intake and Output Flowsheet records that the subject started study drug infusion between 13:00 and 14:00 on 9/17/98. The Telephone Communication Form of 9/18/98 documents that permission was granted not to exceed ——

d. The subjects were to receive study drug by —————— —————— time period. The infusion bag was to be changed after each —— time period. The inspection disclosed that the study drug was not always —————— (Observation #4). For example, the following subjects had interruptions greater than 2 hours:

   i. Subjec —— – Interruption for over 17 hours between infusion bags from 6/22-23/98. The Physician's Patient Clinical History sheet dated 6/22/98 records the firs —— study drug infusion ended at 16:10 on 6/22/98 and the second drug infusion began at 09:20 on 6/23/98.

   ii. Subjec —— – Interruption for 8 hours during the infusion of the first bag on 7/18/98 while taking x-rays.

   iii. Subjec —— – Interruption for over 3 hours between infusion bags. The Patient's Clinical History sheet dated 1/24/99 documents that the second infusion bag was on a different floor.

   iv. Subjec —— – The Nursing Record dated 11/1-2/98 documents an interruption of at least 3.5 hours between drug infusion bags.

Your response letter dated January 11, 2000, does not dispute Observation #4.

e. Several subjects did not have complete laboratory tests performed as per protocol number ——— These laboratory results are an important part of the overall safety assessment of the study drug. The following is a table for all hematology, chemistry, urinalysis, or coagulation tests that were either not done (ND) or were only partially done (P):

SUBJ.#	HEM PRE	HEM DAY 3	HEM DAY 15/DIS	CHEM PRE	CHEM DAY 3	CHEM DAY 15/DIS	URIN PRE	URIN DAY 3	URIN DAY 15/DIS	COAG PRE	COAG DAY 3	COAG DAY 15/DIS
			ND	P	P	ND	ND	ND	ND			ND
		P	ND	P	P	ND		ND	ND			ND
		P	P		P	P		ND	ND			
		P	P		ND	ND		ND	ND			P
		P	P		P	P		ND	ND			
		ND	ND	P	ND	ND		ND	ND		ND	ND
		P	P		P	P			ND			ND
		P			P	P			ND			P
	ND		ND	P	P	ND			ND			ND
			ND		P	ND			ND			NF
					P	P						
			P		P	P						
			P			P						

Legend

Hem.= hematology tests
Chem.= chemistry tests
Urin.= urinalysis
Coag.= coagulation tests
Dis.=discharge
Pre.= pretreatment (screening/baseline)

It is your responsibility as principal investigator to ensure that all tests and evaluations are conducted at the time points indicated in the protocol. Missing tests, tests performed outside of protocol-specified time windows, missed clinical visits (e.g., follow-up visits), and other missing clinical procedures can adversely affect patient safety, as well as data safety and efficacy analyses. Review of laboratory values/results is an essential component of the study to assess the safety and efficacy of the investigational product.

f. Temperature (vital sign) was not always taken as required in the protocol. For example:

SUBJECT	ER ADMISSION	——— INFUSION	— AFTER INFUSION	——→ AFTER INFUSION	AFTER INFUSION	———
	ND	ND	ND			
	ND		ND			
	ND		ND	ND	ND	
	ND	ND	ND			
	ND				ND	

2. **Failure to obtain informed consent in accordance with the provisions of 21 CFR Parts 50 and 56. [21 CFR 312.60]**

Consent forms were not always dated at the time signatures were obtained on the informed consent form by the subject, witness, and/or principal investigator. For example, the dates were missing on the consent forms for the following subjects:

a. Subject # – witness signature
b. Subject # – witness signature
c. Subject # – subject signature
d. Subject # – witness signature
e. Subject # – witness and principal investigator signature
f. Subject # – principal investigator signature
g. Subject # – principal investigator signature

The inspection also disclosed that the subjects signing the informed consent in most cases did not complete dates. It appears that the study coordinator or the person administering the informed consent completed the date. Please explain.

3. **Failure to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation. [21 CFR 312.62(b)]**

a. Source documents were not adequately maintained for all subjects participating in study protocol # ——— Appropriate documentation was not recorded in some charts (i.e., times of study drug administration or completion). Examples include, but are not limited to the following:

i. Subject ——— – The Patient's Clinical History sheet records that the study drug was administered at 09:00 on 7/27/98 and ended at 09:00 on 7/29/98. However, the subject was in the intensive care unit (ICU) during this period of time and only one sheet of the ICU I&O Flowsheet was in the medical record which documents the medication delivered on 7/28/98, 05:00 to 10:00. There is no documentation that study drug was administered during this time or any other time during the subject's stay in the ICU.

ii. Subject ——— - The CRF records that the study drug infusion started at 09:20 on 6/7/98 and ended at 10:00 on 6/9/98. However, there is no documentation in the Nursing Record about the start time of study drug infusion and study drug infusion during an operation from 6/7-8/98.

iii. Subject ——— - The CRF records that the study drug infusion started at 13:30 on 10/31/98 and ended at 13:30 on 11/2/98. However, there is no documentation in the Nursing Record that the study drug was administered from 10/31/98 – 11/1/98.

iv. Subjec —— - The CRF records that the study drug infusion started at 09:30 on 11/28/98 and ended at 10:15 on 11/30/98. However, there is no documentation in the Nursing Record of the study drug administration for this subject.

b. There is no source documentation of the follow-up visits performed at the —— visit for all subjects.

c. The inspection disclosed many discrepancies between information documented in the case report forms and source documents (raw data). Examples include, but are not limited to the following:

i. Subject ——– The CRF indicates the subject's weight as 75 kg; however, the Emergency Medical Service sheet (EMS) documents the weight as 200 lbs. (90 kg) and the Anesthesia Record dated 8/13/98 documents the weight as 100 kg.

ii. Subjec —— - The CRF records the subject's weight 75 kg. However, the EKG sheet dated 4/22/99 documents the weight as 182 lbs. (82 kg) and the EMS sheet dated 4/21/99 documents the weight as 220 lbs. (100 kg); and the Anesthesia Record, dated 4/21/99 documents the weight as 220 lb. (100 kg).

iii. Subject —— – The CRF records the stop time of the first study drug infusion at 13:30 on 11/1/98 and start time of the second infusion bag at 13:30 on 11/1/98. However, the Nursing Record dated 11/1-2/98 (time 17:00) documents that the first infusion bag... "was still running from yesterday and not empty the bag yet." There is no documentation of the stop time.

iv. Subjec —— – The CRF records the time of study drug administration as 12:40 on 9/17/98. However, the I&O Flowsheet records that the study drug infusion began between 13:00 and 14:00 on 9/17/98.

v. Subjec —— – The DEM Trauma Record dated 2/7/99, and Trauma Surgery Service – Consultation/Progress Note dated 2/7/99 record the subject as 47 years old male. The Application Record dated 2/7/99 documents the date of birth to be 12/17/52. However, the CRF documents the date of birth as 11/15/81, a 17 year old.

vi. Subject —— – A memo dated May 14, 1999 indicates that the second —— study drug infusion was given 2 hours late. The CRF documents the first infusion at 09:30 on 11/28/98 and ending at 09:30 on 11/29/98. The second infusion was noted to begin at 10:15 on 11/29/98 ——————.

vii. Subject —— - The CRF documents the initial start of the —— second infusion bag at 21:00 on 7/19/98 and completion at 21:00 on 7/20/98, delivering a total volume infused of 168 ml (7 ml/hour). However, the Nursing Record dated 7/20-21/98 (time 15:00) documents that 150 ml was observed in the intravenous (IV) bag. Based on the subject's weight, the total volume contained in the IV bag should have been 198 ml, and an infusion rate of 7 ml/hour would leave 72 ml at 15:00.

viii. Subject —— – The CRF documents the infusion drug stop time at 23:45 on 03/31/98. However, the I&O Flowsheet documents the stop time between 07:00 and 08:00 on 4/1/98.

ix. Subject —— had a glucose result of 104, per Monitoring Panel, dated 9/26/98 at 07:25, but the CRF reported it as not done.

x. Subject —— The CRF reports that no chest X-ray was taken. However, per the DEM Trauma Record dated 9/16/98, chest X-ray was done in the upright position and the findings are normal.

d. Medical records were missing for the following subjects:

i. Subject ——
ii. Subject ——
iii. Subject —— - Missing Admission, Emergency Room and Trauma Notes
iv. Subject —— - There is no source documentation of the first 2 units of blood transfused to the subject.
v. Subject —— – The Anesthesia Record for the operation from 7/26-27/98 was missing from the medical record.

e. The EMS sheet was not in the medical record for subjects —————— and ——

Source data are all information in original records or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents allow verification of the existence of the subject and substantiate the integrity of data that are collected during a trial. Source documents are crucial, because they show that data have been accurately reported and that the study has been carried out in accordance with the protocol. The clinical investigator is responsible for ensuring the adequacy of the clinical site's source documentation and that data contained in CRFs are complete and accurate.

4. Failure to fulfill requirements for informed consent. [21 CFR 50.20]

The inspection disclosed that some Spanish-speaking subjects signed the English study consent form. There was a Spanish consent form available during the study; however, it was not presented to the subjects. In order to meet the requirements of 21 CFR 50.20, the consent document must be in language understandable to the subject. While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may not be substituted for a written translation.

Your response letter dated January 11, 2000, states that subjects —— and —— were bilingual; however, the discharge summary for each states that the subject was Spanish speaking only.

Deviations in this study appear to be the result of a serious lack of supervision of personnel involved in conducting this study. Staff who were delegated the authority to perform certain functions were not adequately trained and monitored. You should recognize that although authority may be delegated, it is the principal investigator who is ultimately responsible for the conduct of a study. Proper oversight or supervision of medical personnel is necessary to ensure the investigation is conducted according to the protocol. Training and supervision of study personnel are essential to maintain the quality of data collection regarding the conduct of clinical trials. Please provide assurance that study personnel are trained in good clinical practice (GCP).

The lack of supporting raw data for several case report form entries, and the numerous inaccuracies found in the case report forms indicate a lack of attention to effective record keeping practices. All of the information pertinent to the investigation, such as necessary observations and tests, is required to be recorded on the case report forms provided by the sponsor. As the clinical investigator responsible for this and other trials, you must actively review the subject files including case report forms. Investigators are also responsible for supervising the Study Coordinator and other assistants who complete the case report forms and process queries.

Principal investigators may delegate clinical responsibility to other physicians, usually colleagues within their specialty, to residents and fellows, and to nurse practitioners. This downward delegation increases the need for careful supervision of these practitioners. The principal investigator must review their work, particularly their clinical decisions, and must make certain that they are following the study investigational plan (protocol). The principal investigator should meet periodically with the team of clinicians and non-clinicians participating in the study to discuss study progress and problems. Minutes of these meetings should be kept to assure that the principal investigator is effectively managing the study and its participants.

You deviated from an authorized study plan, investigator statement, or other conditions imposed on the study by the sponsor, IRB, or FDA. Your signature on Form FDA 1572, Statement of Investigator, indicates your agreement to comply with all requirements regarding the obligations of clinical investigators conducting human clinical trials and all other pertinent requirements in 21 CFR Part 312.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical study of investigational ——— It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. We request that you inform us, in writing, within fifteen (15) business days after receipt of this letter, of the steps you have taken or will take to correct these violations to prevent the recurrence of similar violations in current and future studies. If corrective action cannot be completed within 15 business days, state the reason for the delay and the time within which the corrections will be completed.

Failure to achieve prompt correction may result in enforcement action without further notice. These actions could include initiation of clinical investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs, a clinical hold, or termination of an investigational new drug application (IND).

Please send your written response to:

Jose Javier Tavarez, M.S.
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Bioresearch Monitoring Team (HFM-650)
1401 Rockville Pike
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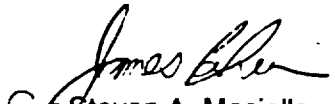
Tel. (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Los Angeles District Office, Director, Compliance Branch, 19900 MacArthur Blvd., Suite 300, Irvine, California 92715. If you require additional time to respond, or have any questions concerning this matter, please contact Mr. Tavarez at the telephone number above.

Sincerely,



Steven A. Masiello
Director
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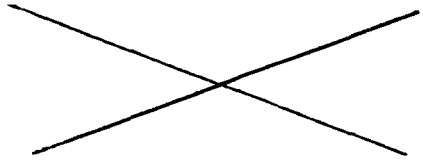
and Research

cc: 

Darcy Spicer, M.D., Chairman
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